Environmental Health Perspectives
Vol. 54, pp. 267–273, 1984

Interaction of Chelating Agents with Cadmium in Mice and Rats

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The influence of several chelating agents (CaDTPA, ZnDTPA, CaEDTA, ZnEDTA, DMSA, D-penicillamine and DMPS, DMP and DDC) on the acute toxicity of $CdCl_2$ and on the whole body retention and tissue distribution of cadmium after the IV application of $^{115m}CdCl_2$ was compared in mice. The chelating agents were applied immediately after the application of cadmium. CaDTPA, ZnDTPA and DMSA appeared to be the most effective antidotes. However, DMSA increased the amount of cadmium retained in kidneys. The treatment of cadmium—poisoned mice with the combination of DMSA (IP) and ZnDTPA (SC) (all the compounds were injected in equimolar dose) decreased the toxicity of cadmium more than treatment with one chelating agents (given in a 2:1 dose). However, by studying the effect of these chelating agents and their combination of the retention and distribution of Cd in mice, it was demonstrated that the combined application of the antidotes showed little or no improvement over the results obtained with the most effective of the individual components. In the urine of rats injected with $CdCl_2$ and treated with the chelating agents (CaDTPA, ZnDTPA, DMSA), the presence of cadmium complexes was demonstrated. The formation of mixed ligand chelates *in vivo* was not proved. Experiments in mice given a single injection of ^{115m}Cd-labeled Cd complexes of DMPS, DMSA and DTPA showed a high retention of cadmium in the organisms after the IV application of CdDMPS and CdDMSA complexes.

Introduction

In previous papers (*1–5*) the effect of calcium and zinc complexes of some aminopolycarboxylic acids (APCA) in acute cadmium intoxication and the effect of these compounds on the excretion and distribution of cadmium were compared. The most effective were CaDTPA and ZnDTPA (*1,2,5*), though CdDTPA was neither the most inert of the cadmium complexes of APCA used nor the least toxic (*3*). It was also reported that *N*-acetyl-D,L-penicillamine had no antidotal activity in cadmium intoxication under the conditions used (*1,2*). The effect of dimercaprol was low (*1,2*).

The purpose of the present studies was to compare the influence of CaDTPA and ZnDTPA on the toxicity, retention and tissue distribution of cadmium with the effects of some chelating agents containing –SH groups. In the light of recent papers which deal with the use of mixed-ligand chelates (*6–9*), the effect of the combination of some chelating agents was studied as well. All the compounds were applied in acute experiments in mice and rats. The chelating agents were injected immediately after the cadmium injection. This enabled study of the interaction of this metal with chelating agents in the organism before cadmium is firmly bound in the tissues. Cadmium retention and distribution after the application of some cadmium chelates was also studied.

Materials and Methods

Male mice (SPF, Velaz Prague) (*20–22 g*) divided into groups of *n* animals (see tables) were used. In the experiment in which the chromatographic analysis of urine was performed as well as in the experiments in which the effect of chelating agents on cadmium-induced lipid peroxidation was examined, male rats (SPF, Velaz, Prague), 130–150 g, were used.

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The following chemicals and drugs were used: $CdCl_2 \cdot 2.5\ H_2O$ (Lachema, puriss.gr.), D-penicillamine (P) (Koch-Light Lab.), dimercaprol (DMP) (BAL, Boots Pure Drug Co. Ltd.), $CaNa_3DTPA$ and $ZnNa_3DTPA$ (prepared in our laboratory from Chel-DTPA, Geigy), $CaNa_2EDTA$ (Edtacal, Spofa) and $ZnNa_2EDTA$ (prepared in our laboratory from Chelaton 2, Lachema), dimercaptopropanesulfonic acid sodium salt (DMPS) (Dimaval, gift from E. Heyl & Co., W. Berlin), *meso*-2,3-dimercaptosuccinic acid (DMSA) prepared by us as sodium salt by dissolving in saline with equivalent amount of $NaHCO_3$ (gift from Fluka AG, Buchs, Switzerland), diethyldithiocarbamate sodium salt (Lachema, puriss.gr.).

In the cadmium excretion and distribution study $^{115m}CdCl_2$ (with carrier) (The Radiochemical Centre, Amersham, England) was used. The radioactivity in the whole body and in various organs after the IV application of 0.5 mg Cd^{2+}/kg (approximately 37 kBq per mouse) was measured by using a scintillation spectrometer with NaI (Tl) detector (*10*). The ^{115m}Cd-labeled complexes of DMPS and DMSA were prepared by the addition of equivalent amounts of these compounds to the $^{115m}CdCl_2$ saline solution. The results are expressed in percent of applied dose.

The same method as described previously (*5,11*) was used for the chromatographic analysis of urine.

The estimation of malondialdehyde as a product of lipoperoxidation was performed in homogenized liver of rats after 2 hr of incubation at pH 7.4 (*12,13*).

The effect of some chelating agents on the renal tissue of cadmium-treated mice was determined. Histopathological study after staining with hematoxylin and eosin and after a special histochemical staining to determine the activity of various intracellular enzymes was performed.

Survival of mice was recorded at the end of 10 days. All results were statistically evaluated (Student's *t*-test, χ^2 test, Fisher's test). The values given are means ± 95% limits.

Results

Influence of Chelating Agents on Acute Toxicity of $CdCl_2$ in Mice

The effect of P, DMP, CaEDTA, ZnEDTA, CaDTPA and ZnDTPA on the cadmium toxicity was compared (Table 1). In this experiment CaDTPA and ZnDTPA appeared to be the most effective antidotes. No protective effect was observed after the administration of ZnEDTA and P.

In the next experiment, the influence of CaDTPA, ZnDTPA, DMPS and DMSA injected in doses corresponding to the various chelator:Cd molar ratios was investigated (Table 2). CaDTPA was the most effective agent of the chelators studied when low doses (1:1, 1:2) were used. No protective effect was observed with administration of DMPS at these lower doses. High protection was seen with DMSA at a dose corresponding to a molar ratio of 5:1. After the application of this higher dose the order of efficacy of chelators was found to be:

DMSA > CaDTPA > ZnDTPA > DMPS.

The result of experiments in which the protective effect of DDC, CaDTPA and ZnDTPA in cadmium intoxication was compared is shown in Table 3. DDC applied simultaneously or 2 hr after the administration of cadmium was ineffective. DTPA complexes provided protection only after the simultaneous application with Cd.

Table 1. Effect of chelating agents on survival of mice injected with $CdCl_2$.[a]

Group and treatment	10 day survival ratio	% survival	Significance (group:group)
1 Cd only	1/20	5	—
2 Cd + D-penicillamine	3/20	15	NS‡
3 Cd + dimercaprol	6/20	30	3:1*
4 Cd + CaEDTA	10/20	50	4:1†
			4:6†
5 Cd + ZnEDTA	5/20	25	NS
6 Cd + CaDTPA	17/20	85	6:1†
			6:4†
7 Cd + ZnDTPA	15/20	75	7:1†

[a]Chelating agents were applied IP immediately following SC injection with $CdCl_2 \cdot 2.5\ H_2O$ (20 mg/kg) at a chelator:Cd molar ratio of 25:1.

*$p < 0.05$.

†$p < 0.01$.

‡NS = $p > 0.05$.

Table 2. Effect of chelating agents given in various doses on survival of mice injected with $CdCl_2$.[a]

Group and treatment	Molar ratio chelator:Cd	10 day survival ratio	% survival	Significance (group:group)
Experiment A				
1 Cd only	—	0/20	0	—
2 Cd + CaDTPA	1:1	20/33	60.6	2:1†
3 Cd + ZnDTPA	1:1	2/33	6.06	NS‡
4 Cd + DMSA	1:1	1/33	3.03	NS‡
5 Cd + DMPS	1:1	0/33	0	NS‡
Experiment B				
6 Cd only	—	0/20	0	—
7 Cd + CaDTPA	2:1	16/20	80	7:6†
				7:8†
				7:9†
8 Cd + ZnDTPA	2:1	4/20	20	8:6*
9 Cd + DMSA	2:1	7/20	35	9:6†
				9:7†
10 Cd + DMPS	2:1	0/15	0	NS‡
Experiment C				
11 Cd only	—	—	0	—
12 Cd + CaDTPA	5:1	27/33	81.82	12:11†
				12:14*
13 Cd + ZnDTPA	5:1	20/33	60.67	13:11†
14 Cd + DMSA	5:1	33/33	100.0	14:11†
				14:12*
15 Cd + DMPS	5:1	4/20	20.0	15:11*

[a]Chelating agents were applied IP immediately following SC injection with $CdCl_2 \cdot 2.5\ H_2O$ (20 mg/kg) at various chelator:Cd molar ratios.
*$p \leq 0.05$.
†$p < 0.01$.
‡NS = $p > 0.05$.

Table 3. Effect of the combination of chelating agents on survival of mice which received $CdCl_2$.[a]

Group and treatment	Molar ratio chelator:Cd	10 day survival ratio	% survival	Significance (group:group)
Experiment A				
1 Cd only	—	0/20	0	—
2 Cd + ZnDTPA	2:1	12/20	60	2:1†
3 Cd + DMSA	2:1	13/20	65	3:1†
4 Cd + ZnDTPA + DMSA	1:1:1	19/20	95	4:2*
				4:3*
Experiment B				
5 Cd only	—	0/20	0	—
6 Cd + CaDTPA	1:1	12/20	60	6:5†
7 Cd + DMSA	1:1	6/20	30	7:5*
8 Cd + CaDTPA + DMSA	0.5:0.5:1	10/20	50	8:6‡
Experiment C				
9 Cd only	—	0/20	0	—
10 Cd + ZnDTPA	2:1	4/20	20	10:9*
11 Cd + DMPS	2:1	0/20	100	NS‡
12 Cd + DMPS + ZnDTPA	1:1:1	0/20	100	NS‡

[a]Chelating agents were applied IP immediately following SC injection with $CdCl_2 \cdot 2.5\ H_2O$ (20 mg/kg) at various chelator:Cd molar ratios.
*$p < 0.05$.
†$p < 0.01$.
‡NS = $p > 0.05$.

Table 4. Effect of simultaneous and subsequent administration of sodium diethyldithiocarbamate (DDC), CaDTPA and ZnDTPA on survival of mice receiving $CdCl_2$.[a]

Group	10 day survival ratio	% survival	Significance (group:group)
Experiment A[b]			
1 Cd only	0/15	0	—
2 DDC	1/15	6,7	NS
3 CaDTPA	13/15	86,7	3:1†
4 ZnDTPA	12/15	80,0	4:1†
Experiment B[c]			
1 Cd only	0+/15	0	—
2 DDC	0+/15	0	NS
3 CaDTPA	3+/15	20	NS
4 ZnDTPA	3+/15	20	NS

[a]Chelating agents were applied IP at chelator:Cd molar ratio of 5:1 after SC administration of $CdCl_2 \cdot 2.5H_2O$ (20 mg/kg).

†$p < 0.01$.

[b]Chelating agents applied immediately following cadmium injection.

[c]Chelating agents applied 2 hr after cadmium injection.

Table 4 shows the results of the experiment in which the combination of ZnDTPA and DTPA was administered. The additive effect of these two chelating agents was demonstrated. This was shown neither after the application of ZnDTPA + DMPS nor after the injection of CaDTPA + DMSA.

Influence of Chelating Agents and Their Combinations on Retention and Tissue Distribution of Cd in Mice

The effect of the chelating agents (P, DMPS, CaDTPA) on the whole body retention and on the content of cadmium in various organs 48 hr after the administration of $CdCl_2$ is shown in Table 5. No effect of P on the cadmium retention was seen. P as well as DMPS enhanced the amount of cadmium retained in kidneys. CaDTPA was found to be the most effective agent of the chelators used in this experiment.

The results obtained in a similar experiment are summarized in Table 6. The influence of DMPS, DMSA, CaDTPA and ZnDTPA on the re-

Table 5. Effect of chelating agents on total body burden and tissue content of cadmium in mice 48 hr after the application of $CdCl_2$.[a]

Group and treatment	Total body burden of cadmium, %[b]	Cd content of tissues, %[b]		
		Liver	Gastrointestinal tract	Kidneys
1 Cd only	78.50 ± 5.20	44.24 ± 3.20	7.10 ± 2.00	2.67 ± 0.70
2 Cd + D-penicillamine	80.70 ± 3.10	41.52 ± 2.63	6.20 ± 1.32	6.55 ± 1.70*
3 Cd + dimercaprol	48.30 ± 4.30	25.18 ± 1.91	1.94 ± 0.40	6.74 ± 0.93*
4 Cd + CaDTPA	12.70 ± 1.43	7.74 ± 0.54	0.89 ± 0.28	0.64 ± 0.10*

[a]Chelating agents were applied IP immediately following IV injection of $^{115m}CdCl_2 \cdot 2.5\ H_2O$ (0.5 mg Cd/kg) at a chelator:Cd molar ratio of 50:1; $n = 7$ for each group.

[b]Expressed as % of dose applied; values represent the mean ± 95% confidence limits.

*Significantly different from the control at $p < 0.05$.

Table 6. Effect of chelating agents and their combination on total body burden and tissue content of cadmium in mice 24 hr after the application of $CdCl_2$.[a]

Group and treatment	Total body burden of Cd, %[b]	Cd content of tissues, %[b]		
		Liver	Gastrointestinal tract	Kidneys
1 Cd only	89.57 ± 6.10	52.22 ± 5.63	10.25 ± 1.13	6.35 ± 0.91
2 Cd + DMPS IP	83.28 ± 7.80	41.67 ± 4.61*	7.34 ± 0.80*	8.83 ± 1.12
3 Cd + CaDTPA SC	33.38 ± 9.15*	17.33 ± 5.36*	3.41 ± 1.08*	3.87 ± 1.18*
4 Cd + CaDTPA SC + DMPS IP	24.50 ± 4.40*	13.52 ± 3.48*	2.40 ± 0.74*	2.75 ± 0.54*
5 Cd + DMSA IP	64.51 ± 7.21*	28.23 ± 4.64*	6.16 ± 1.07*	9.73 ± 1.32
6 Cd + CaDTPA SC + DMSA IP	22.01 ± 2.10*	9.52 ± 1.53*	2.30 ± 0.27*	3.21 ± 0.42*
7 Cd + ZnDTPA SC	44.73 ± 2.84*	24.82 ± 1.79*	5.12 ± 0.70*	4.05 ± 1.04*

[a]Chelating agents were applied IP immediately following the IV injection of $^{115m}CdCl_2 \cdot 2.5\ H_2O$ (0.5 mg Cd/kg) at a chelator:Cd molar ratio of 10:1; $n = 8$ for all groups.

[b]Expressed as % of dose applied; values represent the mean ± 95 confidence limits.

*Significantly different from the control at $p < 0.05$.

Table 7. Effect of chelating agents and their combination on total body burden and tissue content of cadmium in mice 24 hr after the application of $CdCl_2$.[a]

Group	Molar ratio chelator:Cd	Total body burden of Cd, %[b]	Cd content of tissues, %[b]		
			Liver	Gastrointestinal tract	Kidneys
1 Cd only	—	88.12 ± 4.85	42.91 ± 5.27	11.15 ± 1.38	4.86 ± 1.49
2 Cd + DMSA SC	5:1	71.38 ± 8.34*	35.81 ± 6.10*	6.99 ± 1.51*	10.36 ± 3.47*
3 Cd + ZnDTPA IP	5:1	57.79 ± 7.13*	31.84 ± 7.27*	7.12 ± 1.73*	5.59 ± 0.97
4 Cd + ZnDTPA IP + DMSA SC	5:5:1	59.53 ± 6.77*	29.32 ± 4.54*	6.26 ± 1.37*	7.96 ± 2.24*
5 Cd + ZnDTPA IP	10:1	33.49 ± 4.54*	16.50 ± 5.43*	3.91 ± 1.61*	3.01 ± 0.54*
6 Cd + CaDTPA IP	5:1	37.63 ± 9.77*	22.94 ± 6.93*	3.94 ± 1.13*	2.09 ± 1.09*

[a]Chelating agents were applied immediately following the IV injection of $^{115m}CdCl_2 \cdot 2.5\ H_2O$ (0.5 mg Cd/kg) at various chelator: Cd molar ratios; $n = 7$ for all groups.
[b]Expressed as % of dose applied; values represent the mean ± 95% confidence limits.
*Significantly different from the control at $p < 0.05$.

tention and distribution of cadmium was determined. The most effective appeared to be CaDTPA and the DMSA + CaDTPA combination. No increase in excretion of cadmium was seen after DMPS. However, treatment with this chelating agents significantly reduced the amount of cadmium found in the liver and gastrointestinal tract and increased the amount of cadmium in kidneys and in other organs. Similarly, all the compounds used decreased the amount of cadmium in the liver and in the gastrointestinal tract. DMSA increased the amount of cadmium retained in the kidneys. The agents which decreased the content of cadmium in the kidneys were CaDTPA, ZnDTPA and the combinations CaDTPA + DMPS and CaDTPA + DMSA.

The results obtained in the experiment in which the effect of the combination of ZnDTPA and DMSA was examined are shown in Table 7. The influence of this combination on the cadmium retention was compared with the effects of single agents given alone.

ZnDTPA applied at a dose of 5:1 was not effective. The effect of the combination ZnDTPA + DMSA was not better than that of ZnDTPA. DMSA increased the content of cadmium in the kidneys in all cases. The effect of CaDTPA (5:1) was the same as that of ZnDTPA (10:1). The amount of cadmium retained in the liver was decreased after the application of the compounds.

Another experiment demonstrated (Table 8) that the combination of ZnDTPA + DMSA (5:5:1) is more effective than DMSA (10:1). However, the effect of that combination did not reach the effect of ZnDTPA (10:1). After the application of DMSA (either alone or in combination) the content of cadmium in the kidneys was elevated.

Chromatographic Analysis of Rat Urine after Administration of $CdCl_2$ and Chelating Agents

In the urine of rats given $CdCl_2 \cdot 2.5\ H_2O$ (10 mg/kg, SC) and treated with CaDTPA, ZnDTPA, DMSA (5:1) or with the combination of CaDTPA + DMSA and ZnDTPA + DMSA (5:5:1) the Cd complexes of DMSA and DTPA were detected by paper chromatography. The properties of CdDMSA complexes are different from those of CdDTPA. An extremely slow flow rate of

Table 8. Effect of chelating agents and their combination on total body burden and tissue content of cadmium in mice 24 hr after the application of $CdCl_2$.[a]

Group	Molar ratio chelator:Cd	Total body burden of Cd, %[b]	Cd content of tissues, %[b]		
			Liver	Gastrointestinal tract	Kidneys
1 Cd only	—	88.12 ± 4.85	42.91 ± 5.27	11.15 ± 1.38	4.86 ± 1.49
2 Cd + ZnDTPA IP	10:1	33.45 ± 2.36*	16.50 ± 5.50*	3.91 ± 2.30*	3.01 ± 0.54*
3 Cd + DMSA SC	10:1	60.81 ± 2.73*	23.11 ± 3.81*	4.80 ± 0.70*	10.53 ± 1.99
4 Cd + ZnDTPA IP + DMSA SC	5:5:1	50.36 ± 4.66*	17.84 ± 5.10*	5.62 ± 0.50*	8.04 ± 0.66*

[a]Chelating agents were applied immediately following the IV injection of $^{115m}CdCl_2 \cdot 2.5\ H_2O$ (0.5 mg/kg) at various chelator: Cd molar ratios; $n = 8$ for all groups.
[b]Expressed as % of dose applied; values represent the mean ± 95% confidence limits.
*Significantly different from the control at $p < 0.05$.

Table 9. Effect of chelating agents on cadmium-induced lipid per oxidation in kidneys of rats 48 hr after application.[a]

μg malondialdehyde/g tissue[b]				
Control	Cd	Cd + CaDTPA	Cd + ZnDTPA	Cd + DMSA
38.7 ± 5.7 $n = 8$	89.8 ± 9.8* $n = 5$	33.6 ± 4.8 $n = 8$	31.4 ± 9.8 $n = 8$	46.0 ± 13.3 $n = 8$

[a]Chelating agents were applied IP immediately following the SC injection of $CdCl_2 \cdot 2.5\ H_2O$ (7.5 mg/kg) at a chelator: Cd molar ration of 5:1.
[b]Mean values ± 95% confidence limits.
*Significantly different from the control at $p < 0.05$.

CdDMSA was found. The independent formation of CdDTPA in the presence of DMSA was demonstrated. The formation of mixed ligand chelates was not proved.

Influence of Chelating Agents on Lipid Peroxidation

The influence of chelating agents on cadmium-induced lipid peroxidation in kidneys of rats 48 hr after administration of Cd shows that the lipid peroxidation in kidney homogenates is significantly elevated. All the chelating agents used (CaDTPA, ZnDTPA, DMSA) were effective in preventing cadmium-induced lipid peroxidation (Table 9).

Histopathological Examination of Mouse Renal Tissue

In a preliminary experiment, mice were injected with $CdCl_2 \cdot 2.5\ H_2O$ at in a dose of 5 mg/kg SC alone or in the combination with the chelating agents CaDTPA, ZnDTPA or DMSA (5:1 IP). The kidneys were removed 48 hr after the treatment. No histopathological changes were found in any case when the hematoxylin and eosin staining was used. A slight reduction of the activity of acid phosphatase in cells of the tubules was demonstrated after the application of cadmium and CaDTPA. No changes in the activity of glutamate dehydrogenase, α-glycerol phosphate dehydrogenase and nicotinicadenine dinucleotide reductase were found.

Retention and Tissue Distribution of Cd after Administration of Cd Chelates

In this experiment, $^{115m}CdCl_2$ and ^{115m}Cd-labeled cadmium chelates were administered IV to mice. The results are shown in Table 10. The highest cadmium excretion was found after the injection of CdDTPA. The total body burden of cadmium after the administration of Cd $(DMPS)_1$ and CdDMSA complexes did not differ significantly from that estimated after the administration of $CdCl_2$. The whole body retention of cadmium after the administration of Cd $(DMPS)_3$ was lower than that of the controls. The amount of cadmium retained in the kidneys was elevated after the injection of Cd $(DMPS)_3$, Cd$(DMSA)_1$ and Cd$(DMSA)_3$.

Discussion and Conclusions

The results confirm our earlier findings with regard to the efficiency of CaDTPA and ZnDTPA in acute cadmium intoxication (*5*). DMSA was more effective than CaDTPA when applied in

Table 10. Total body burden and tissue content of cadmium in mice 24 hr after the application of $CdCl_2$ and Cd chelates.[a]

Group and treatment	Total body burden of Cd, %[b]	Tissue content of Cd, %[b]		
		Liver	Gastrointestinal tract	Kidneys
1 $CdCl_2$	94.30 ± 4.47	59.31 ± 6.38	9.58 ± 1.48	6.07 ± 1.02
2 Cd$(DMPS)_1$	93.02 ± 7.02	54.07 ± 8.58	9.33 ± 2.36	7.37 ± 1.32
3 Cd$(DMPS)_3$	82.47 ± 5.02	38.59 ± 2.38*	8.13 ± 1.47	10.87 ± 1.91
4 Cd$(DMSA)_1$	95.75 ± 5.02*	55.46 ± 6.92	6.50 ± 1.71*	7.63 ± 1.55*
5 Cd$(DMSA)_3$	95.89 ± 5.81	53.94 ± 8.23	7.24 ± 1.16*	8.14 ± 1.43*
6 CdDTPA	66.31 ± 6.87*	37.53 ± 3.89*	6.39 ± 1.28	5.92 ± 1.51

[a]The $^{115m}CdCl_2$ and ^{115m}Cd chelates were applied IV at a dose of 0.5 mg Cd/kg; $n = 8$ for all groups.
[b]Expressed as % of dose applied; values represent the mean ± 95% confidence limits.
*Significantly different from the control at $p < 0.05$.

higher doses. However, the content of cadmium in the kidneys was elevated after the application of this agent. Our results are in agreement with the finding of other authors (*8,9,14,15*). However, we were not able to demonstrate a positive effect of DMSA on the cadmium content in the kidneys (*14*). All the chelating agents containing sulfhydryl groups increase the cadmium content in the kidneys.

We were unable to confirm the increase in the effectiveness of DDC as an antidote when treatment is delayed after administration of cadmium (*16,17*). The effectiveness of the DTPA complexes decreases with increasing interval between the injection of cadmium and these agents. This result is in agreement with our earlier findings (*4*).

The mobilizing and protective effect of ZnDTPA in cadmium intoxication is based predominantly on the kinetic lability of this complex which facilitates the exchange of the metal bound in chelate (pseudoisotopic exchange) (*5*).

Neither the formation of mixed ligand chelates *in vivo* nor the potentiation of the effectiveness after the simultaneous application of two chelators was shown. Only the combination of ZnDTPA + DMSA in acute cadmium intoxication improved the effect achieved with one chelator alone.

There is considerable speculation and controversy regarding the mode of toxic action of heavy metals. One mechanism suggested is that toxicity of some heavy metals may be mediated through peroxidation of membrane lipids. We have demonstrated the cadmium-induced lipid peroxidation in liver of rats. This effect of cadmium was vitiated by the pretreatment with zinc chloride (*13*). The protective effect of chelating agents on the cadmium-induced lipid peroxidation in kidneys was demonstrated.

Even though the amount of cadmium in kidneys is enhanced due to DMSA in mice, the cadmium-induced lipid peroxidation in kidney tissue was decreased after the administration of cadmium and DMSA in rats. The properties of the CdDMSA complex formed in course of the detoxication of cadmium merit further examination.

The protective effect of DMSA in cadmium-induced lipid peroxidation is probably caused by the binding of cadmium. However, a direct effect of DMSA on the lipid peroxidation is not excluded.

The results of our experiments form a basis for the selection of agents which might be used in further studies of the mobilization of cadmium from old deposits in the organism.

The authors wish to thank E. Heyl & Co, W. Berlin, for sodium 2,3-dimercaptopropanesulfonate (DMPS, Dimaval) and the Fluka AG, Buchs, Switzerland for their *meso*-2,3-dimercaptosuccinic acid. Skillful technical assistance by Miss Jiřina Svačinová, Mrs. Ivana Sedláčková, Mrs. Jana Adamcová, Mrs. Irena Makrlíková and Mrs. Blanka Šafářová is gratefully acknowledged.

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